TRANSLATION

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Description

Computer for analyzing data from measurements of nuclear magnetic resonance, nuclear magnetic resonance tomograph provided with said computer, and method for analyzing data from measurements of nuclear magnetic resonance

The invention pertains to a computer for analyzing data from measurements of nuclear magnetic resonance, whereby the data contains at least one relaxation signal of a sample.

The invention also relates to a nuclear magnetic resonance tomograph and to a method for analyzing data from measurements of nuclear magnetic resonance, a process in which at least one relaxation signal of a sample is determined.

Nuclear magnetic resonance (NMR) is employed in order to obtain a contrast image of an object or spectroscopic information about a substance. Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) make it possible to examine regional hemodynamics *in vivo* with changes in blood volumes and blood states as well as changes in the metabolism as a function of brain activity; see: S. Posse *et al.*: Functional Magnetic Resonance Studies of Brain Activation; Seminars in Clinical Neuropsychiatry, Vol. 1, No. 1, 1996, pages 76 through 88.

Particularly in medical research, there is a need to acquire information about brain activity by means of measurements of blood flow or changes in the concentration of deoxyhemoglobin. Neuronal activation is manifested by an increase of the blood flow into activated regions of the brain, whereby a drop occurs in the concentration of deoxyhemoglobin. Deoxyhemoglobin (DOH) is a paramagnetic substance that reduces the magnetic field homogeneity and thus accelerates the signal relaxation. If the DOH concentration drops due to brain activity that triggers blood flow, then the signal relaxation in the active regions of the brain is modulated. It is primarily the protons of hydrogen in water that are excited. A localization of brain activity is made possible by conducting an examination with functional NMR methods that measure the NMR signal with a time delay (echo time). This is also referred to as a susceptibility-sensitive measurement. The biological mechanism of action is known in the literature under the name

BOLD effect (Blood Oxygenation Level Dependence effect) and, in susceptibility-sensitive magnetic resonance measurements at a field strength of a static magnetic field of, for example, 1.5 tesla, it leads to fluctuations of the image brightness of up to 10% in activated regions of the brain. Instead of the endogenous contrast agent DOH, other contrast agents can also occur that cause a change in the susceptibility. NMR imaging methods select slices or volumes that yield a measurement signal under appropriate irradiation with high-frequency pulses and under the application of magnetic gradient fields; this measurement signal is digitized and stored in a two-dimensional or three-dimensional field in the measuring computer.

A two-dimensional or three-dimensional Fourier transform on the basis of the raw data collected then serves to acquire (reconstruct) the desired image information.

A reconstructed slice image consists of pixels (picture elements), and a volume data set consists of voxels (volume elements). A pixel is a two-dimensional picture element, for instance, a square. The image is made up of the pixels. A voxel is a three-dimensional volume element, for example, a cube which, for metrological reasons, does not exhibit any sharp boundaries. The dimensions of a pixel normally lie in the order of magnitude of 1 mm^2, and those of a voxel in the order of magnitude of 1 mm^3. The geometries and dimensions can vary.

Since experiments have shown that it is never possible to assume a strictly two-dimensional plane in the case of slice images, the term voxel is often employed here as well since this takes into consideration the fact that the image planes extend into the third dimension.

By comparing the measured signal course in every pixel with the time course of a model function, a stimulus-specific neuronal activation can be detected and spatially localized. A stimulus can be, for instance, a somatosensorial, acoustic, visual or olfactory stimulus as well as a mental or motor task. The model function or the model time series describes the anticipated signal change of the magnetic resonance signal resulting from neuronal activation. These can be derived, for example, by means of empirical rules from a paradigm of the experiment in question. The essential aspect is to take into consideration a time delay of the model function with respect to the paradigm (sluggish reaction of the blood flow in response to neuronal activation).

It is already known how brain activation can be depicted by activation images acquired from nuclear spin tomographic data. The activation images can even be com-

puted and displayed in real time, that is to say, a data set can be converted into an image before the next data set is measured. Here, the time interval is typically 1 to 3 seconds.

Such a computation and reproduction of the activation images in real time are described in US patent no. 5,657,758. This method is characterized by the fact that it allows a high resolution, both in terms of time and space.

Another known method is presented in the articles by Jezzard, P. *et al.*, Proc. SMRM 1993, page 1392; Biswal, B. *et al.*, MRM 34 (1995) page 537 and Purdon, P. *et al.*, Proc. ISMRM 1998, page 253. This method makes use of a measuring signal and a paradigm of the measurement. Both signals undergo a Fourier transform.

The known methods analyze the similarity between the signal of the paradigm and of the measured data.

The invention has the objective of carrying out a method of the known type in such a way that the highest possible contrast-to-noise ratio is achieved.

According to the invention, this objective is achieved in that a computer of the known type is configured in such a way that the computer operates with at least one analyzing means, whereby said analyzing means separates the data into at least two parts that are differently dependent on an echo time T_E.

In particular, the invention provides for a computer with which a fast spectroscopic imaging method can be realized that detects the changes in the NMR signal relaxation using a time constant $T_2^* = \frac{1}{R_2^*}$ at several points in time following excitation.

This spectroscopic imaging method is preferably an echo-planar imaging method, especially a repeated two-dimensional echo-imaging method consisting of a repeated use of two-dimensional echo-planar image encoding. Spatial encoding takes place within the shortest possible time span that is repeated several times during one signal decay and preferably ranges from 20 ms to 100 ms. The multiple repetition of the echo-planar encoding during one signal decay depicts the course of the signal decay in the sequence of reconstructed individual images.

A practical conventional echo-planar method is designated as EPI (Echo-Planar-Imaging). An advantageous implementation of the method according to the invention is done by means of TURBO-PEPSI (Proton Echo Planar Spectroscopic Imaging).

The number of images that are encoded during the signal decay is dependent on the relaxation time and on the encoding time Δt for a single image.

Preferably, a computer is used to analyze data from nuclear magnetic resonance tomography, a process in which the data contains at least one relaxation signal of a sample and in which the data is separated into parts that are dependent on an echo time T_E and into at least one more component that is not dependent on the echo time T_E and whereby the signals that are dependent on an echo time T_E are acquired as activation signals.

A noise signal can be detected in that the computer operates with at least one analyzing means which separates the data into at least one part that is dependent on an echo time T_E and into another component that is not dependent on the echo time T_E, whereby the analyzing means acquires signals that are dependent on an echo time T_E as activation signals.

A separation of several components of a function to be examined can be ascertained by determining the signals that have a different dependence on the echo time T_E. Thus, it is possible, for instance, to separate an amplitude s_0 from a time constant T_2^* and/or from a noise signal g.

Moreover, the invention relates to a nuclear magnetic resonance tomograph that comprises at least one computer according to the invention.

The invention also provides that a method to analyze data from nuclear magnetic resonance tomography – whereby at least one relaxation signal of a sample is determined – is carried out in such a way that the data is separated into at least two parts having a different dependence on an echo time T_E.

Preferably, the process is to be carried out in such a way that intensity values of the measured data for identical echo times are acquired in at least two different recordings of the relaxation signal and in that a dependence of the intensity values on the echo time T_E is subsequently acquired and in that the relaxation signal is separated into parts having a different dependence on the echo time T_E.

Preferably, the method should be carried out in such a way that the relaxation signal is divided into a part that is dependent on an echo time T_E and into at least one part that is not dependent on the echo time T_E and so that the part that is dependent on the echo time T_E is acquired as an activation signal.

In this context, it is especially advantageous for at least one signal to be detected that is proportional to $T_E \exp(-T_E / T_2^*)$, whereby the value of T_2^* is determined particularly by means of a preferably separate fit procedure on the basis of the same data.

Here, it is particularly practical for T_2^* to be calculated with the following formula: $S = S_0 \exp(-T_E / T_2^*) + g$.

Furthermore, it is advantageous to carry out the method in such a way that the statistical fluctuations of ΔT_2^* are determined.

In this context, it is especially practical for a standard deviation $\sigma(\Delta T_2^*)$ to be calculated.

It is likewise advantageous for a quotient $\sigma(\Delta T_2^*) / T_2^*$ to be formed and acquired as a measure of an activity.

Here, it is particularly practical for a statistical deviation of an initial intensity S_0 to be determined.

Here, it is advantageous for a standard deviation $\sigma(S_0)$ to be calculated.

In this context, it is preferable for a quotient $\sigma(S_0) / S_0$ to be calculated.

Particular preference is given to carrying out the method in such a way that a statistical fluctuation of a noise signal g is determined.

Here, it is especially advantageous for a standard deviation $\sigma(g)$ of g to be formed.

Moreover, the method is preferably carried out in such a way that the recorded data is acquired in an at least two-dimensional field, whereby a field axis (DTE) acquires echo times T_E and whereby another field axis (DTR) reproduces repetitions of excitations at a time interval T_R.

Here, it is particularly advantageous for $\sigma(\Delta T_2^*)$ and $\sigma(g)$ to be determined by means of the following steps:

(i) adaptation of signals averaged over the other field axis (DTR) to an exponential decay as a function of the first field axis (DTE) and determination of S_0 and T_2^*;

(ii) calculation of $\sigma(\Delta S_0)$, $\sigma(\Delta T_2^*)$ and $\sigma(g)$ for several voxels and different T_E, followed by averaging of these values over at least one region of interest (ROI);

(iii) adaptation of

$$\frac{\sigma(\Delta S)}{S_0} = \left\{\left[\left(\frac{T_E}{T_2^*}\right)^2\left(\frac{\sigma(\Delta T_2^*)}{T_2^*}\right)^2 + \left(\frac{\sigma(\Delta S_0)}{S_0}\right)^2 - 2\frac{T_E}{T_2^*}\frac{\langle \Delta S_0 \Delta T_2^* \rangle}{S_0 T_2^*}\right] e^{-2T_E/T_2^*} + \left(\frac{\sigma(g)}{S_0}\right)^2\right\}^{1/2}$$

and determination of $\sigma(\Delta S) / S_0$ as a function of T_E.

Here, it is particularly advantageous for the expression $\langle \Delta S_0 \Delta T_2^* \rangle = 0$ to be used for the adaptation of $\sigma(\Delta S_0) / S_0$.

Additional advantages, special features and practical refinements of the invention can be gleaned from the subordinate claims and from the following presentation of preferred embodiments of the invention with reference to model calculations, drawings and a table.

The drawings show the following:

Figure 1 – multi-echo sequence with several measuring sequences, each of which follows a spin excitation (*) and involving the acquisition of various echo times T_E;

Figure 2 – a schematic diagram that serves to illustrate a method involving the separate preparation of data for each of the echo times;

Figure 3 – an experimental differential signal of a functional relaxation time change in a selected picture element as a function of the measuring time following a signal excitation;

Figure 4 – ΔS from various voxels averaged over a few ROIs as a function of T_E for two representative persons;

Figure 5 – in the upper portion of the image, a detection of brain activation in four steps by means of a conventional imaging method and, in the lower portion of the image, a detection of brain activation by means of a method according to the invention.

The table shows a compilation of the experimental sample data.

Figure 1 depicts a multi-echo sequence with several measuring sequences, each of which follows a spin excitation (*) and involving the acquisition of various echo times T_E.

The measuring sequences of the multi-echo sequence were determined by means of the Turbo-PEPSI method. Each of the measuring sequences contains twelve echo sig-

nals with echo times that lie between 12 and 213 ms. The echo times were each acquired in the form of a time interval ΔT_E lasting 18.3 ms.

The values given for the echo times and the time intervals are each adapted to the speed of the data processing. Particularly in the case of a further improvement in scanner technology, it will be possible to raise the number of echo signals and to shorten the time intervals ΔT_E.

Figure 2 depicts a schematic diagram showing how differing measuring sequences are used to acquire a signal at a first echo time or at a second or subsequent echo time.

In the curve depicted in Figure 3, a measuring signal σ (S) has been acquired as a function of the echo time. It shows a principle involving a fit procedure that serves to divide the measuring signal σ (S) into components that are dependent on T_2^* and into noise that is not dependent on T_E. The measuring signal σ (S) consists of a part that is dependent on an amplitude S_0 and of a part that is dependent on a relaxation time T_2^* and of a constant noise signal g.

In particular, the invention provides for achieving a differentiation between activation signals and noise by means of an analysis of the course of time of the measured data and/or their statistical distribution.

The analysis method according to the invention can be checked experimentally, for example, by means of nuclear spin tomographic examinations of the brains of test subjects. A source of light, especially a matrix of light-emitting diodes (LED), is positioned directly in front of the face of the test subjects and then excited so as to emit flash signals. The frequency of excitation is 8 Hz. The effect of the signal flashes is exerted over a time interval – synchronized with the carrier signal from a scanner – of several seconds, for instance. 5 seconds. which is followed by a rest interval of approximately the same duration. The scanner is a Vision 1.5 Tesla, full-body scanner made by Siemens Medical Systems of Erlangen, Germany, with a magnetic field gradient of 25 mT/m. Such a scanner is able to switch over gradient fields within about 600 µs.

TURBO-PEPSI (Proton Echo Planar Spectroscopic Imaging) was employed as the spectroscopic imaging method.

Data adaptation was performed according to the exponential function:

$$S = S_0 e^{-T_E/T_2^*}$$

making use of a non-linear least-square-fit.

A differentiation between activation and noise by means of multi-echo fMRI will be presented below.

The detection of physiological noise (caused, for example, by heart beat) calls for a stationary frequency spectrum, for adequate temporal resolution as well as for prior knowledge about the spatial and temporal characteristics of the noise. According to the invention, a new method for differentiating between BOLD-related variations and other fluctuations of the MR signal (caused, for instance, by thermal noise) is being proposed that can completely do without any prior knowledge of a stimulation paradigm. This method is based on a single-shot-multi-echo sequence like the Turbo-PEPSI technique described in the article by Posse, S. *et al.* in PROC. ISMRM 1998, page 299. Reference is hereby made to the entire text of this publication.

Following signal excitation, its relaxation behavior is recorded at equidistant time intervals T_E. This is repeated several times at time intervals of T_R seconds. In such an experiment, the signal of each voxel forms a two-dimensional field with the echo times T_E in one direction (DTE) and with the repetitions at the time interval T_R in the other direction (DTR). The relaxation is assumed to be monoexponential, $S = S_0 \exp(-T_E / T_2^*) + g$, with a hardware-dependent noise g that we can consider as white in both domains, DTE and DTR. The values S_0 and T_2^* are constant in DTE but they vary in DTR: S_0, for instance, due to hardware instabilities or blood flow effects and T_R, for instance, due to the test subject stimulation. Variations in T_2^* indicate changes in the local blood flow. In the case of relatively small changes ΔS_0 and ΔT_2^*, the signal changes can be formulated as follows:

$$\frac{\Delta S}{S_0} = \left\{ \left[\left(\frac{T_E}{T_2^*} \right)^2 \left(\frac{\sigma(\Delta T_2^*)}{T_2^*} \right)^2 + \left(\frac{\sigma(\Delta S_0)}{S_0} \right)^2 - 2 \frac{T_E}{T_2^*} \frac{\langle \Delta S_0 \, \Delta T_2^* \rangle}{S_0 \, T_2^*} \right] e^{-2 T_E / T_2^*} + \left(\frac{\sigma(g)}{S_0} \right)^2 \right\}^{1/2} \quad [1]$$

wherein $\langle A \rangle$ and $\sigma(A)$ correspond to the mean value and to the standard deviation of a quantity A in DTR. Further analysis depends on the actual magnitude of the terms used in [1]. It is practical, under experimental conditions, for ΔS_0 to be negligible both in the resting and in the activation phases (except in the sagital sinus). The quantities $\sigma(\Delta T_2^*)$ and $\sigma(g)$ are determined as follows: (i) adaptation of the signal averaged over the DTR to the monoexponential decay as a function of DTE in order to determine S_0 and T_2^*; (ii) calculation of $\sigma(\Delta T_2^*)$ and $\sigma(g)$ for each voxel and for each T_E and averaging of those values over the region of interest (ROI); (iii) adaptation of [1] with $\Delta S_0 = 0$ to these val-

ues as a function of T_E. This is possible because local brain activation is manifested by an increase of T_2^*, which displays a characteristic T_E-dependence proportional to $T_E e^{-T_E/T_2^*}$, in contrast to which the value of the white noise does not depend on T_E (see figures). The T_E-dependence of the signal outside of the brain is approximated by a constant. In order to validate this method, the quantity of white noise is compared to the noise outside of the brain, taking into consideration that σ (g) is reduced outside of the brain. For a Gaussian distribution, this reduction factor is 0.6028.

Visual stimulation experiments involving four healthy test subjects were carried out employing a Siemens Vision-1.5-Tesla scanner. By means of a multi-layer Turbo-PEPSI sequence, 12 EPI images (matrix size: 64 × 32 pixels; pixel size: 3 × 6 mm²) were acquired of a single FID, 90° flip angle at echo times ranging from 12 to 228 ms. A conventional correlation analysis was carried out with the Stimulate software package, with the use of a boxcar reference vector.

Figure 4 shows ΔS from various voxels averaged over a few ROIs as a function of T_E for two representative persons. The variability of all values over ROIs was small (10% to 20%). The ROIs were located in the visual cortex (vc), in the motor cortex (mc), in the white matter (wm) and outside of the brain, circumventing areas outside of the brain that are characterized as phantom images (out). The filter results from [1] are compiled in the table; wherever the abbreviated ROI designations are followed by the number of voxels between parentheses, the mean correlation coefficient is normalized over a ROI, σ (g) of the ROI outside of the brain, to the mean S_0 of the inner ROIs and the errors in all values are defined as a standard deviation.

Table 1

ROI			
vc (20)	0.62 ± 0.21	4.3 ± 0.1	0.75 ± 0.05
mc (20)	−0.11 ± 0.14	0.26 ± 0.16	0.79 ± 0.05
wm (21)	−0.009 ± 0.19	−0.001 ± 5	0.93 ± 0.07
out (21)	−0.19 ± 0.11	not fitted	0.66 ± 0.01
vc (28)	0.67 ± 0.12	3.6 ± 0.1	0.42 ± 0.07
mc (32)	−0.22 ± 0.14	−0.6 ± 0.8	0.72 ± 0.06
wm (32)	−0.29 ± 0.06	−0.4 ± 1.2	0.64 ± 0.06
out (38)	−0.12 ± 0.25	not fitted	0.45 ± 0.01

For all persons, the value of $\sigma\ (\Delta T_2^*) / T_2^*$ in the activated voxels was significantly increased, in contrast to which there was no significant deviation from 0 in the non-activated voxels. This is why this value has a determining character with a negligible stochastic component.

Consequently, $\sigma\ (\Delta T_2^*) / T_2^*$ is as suitable as an indicator of regional brain activity as the correlation coefficients of a conventional correlation analysis. In contrast to the latter, however, $\sigma\ (\Delta T_2^*) / T_2^*$ displays brain activity for any desired stimulation course, so that it is not necessary to have knowledge of a paradigm. The slight variability of this value over the ROIs would seem to indicate that the results for individual voxels are similar to those presented here. This allows the creation of $\sigma\ (\Delta T_2^*) / T_2^*$ maps. The level of the T_E-independent white noise is very low, which allows the assumption that it stems from the hardware. The S_0 noise is so small that a more precise examination of the S_0 noise is difficult in view of the white noise that is present.

The invention provides for a method for the differentiation between an activation, especially a brain activation and noise, whereby no correlation analysis is required. Naturally, the invention can also be employed in combination with a correlation analysis such as, for example, a calculation of correlation coefficients, Z scores or the application of a t-test, so as to be able to check the results obtained in this manner. However, there is no need for a correlation analysis with two different measurements, one of which takes place with stimulation while the other takes place without stimulation. For comparison purposes, however, it is possible to include a correlation analysis in which correlation coefficients between the course of time of the stimulator ("reference vector") and signal changes in pixels of the image are ascertained.

High values for the correlation coefficient ascertained in this process can be regarded as an activity indicator and reproduced as additional information in slice images or volume images, for instance, in the case of a graphic representation of the measured data.

The invention is particularly well-suited for applications in areas where complicated activations take place. For this reason, the method according to the invention and the computer according to the invention are especially suitable for analyzing higher cognitive brain functions, such as emotions, memory and imagination.

The invention entails numerous advantages. These include an optimization of the measuring sensitivity for a quantitative measurement of the relaxation time and of the

qualitative relaxation time change. This allows the use of imaging having the highest possible bandwidth (shortest encoding time) for the smallest spatial distortion possible and also to achieve maximum measuring sensitivity by measuring an optimal number of encodings following signal excitation.

The analysis method can be used in real time measurements in order to directly analyze the relaxation changes.

In addition, the analysis methods according to the invention are particularly versatile. It has been proven to be practical to employ a summation or, even more advantageously, a weighted summation which, in comparison to a curve adaptation, can be done faster and without any loss of the measuring sensitivity. A summation, or a weighted summation, has the advantage that it constitutes a particularly reliable analysis method.

All of the test subjects exhibited a strong activation in the primary visual cortex (V_1) and in the neighboring regions. The changes observed in the functional signal measured with TURBO-PEPSI amount to up to 10%, depending on the relaxation time T_2^*, the position and the test subject in question.

The excitation exhibits a maximum in the vicinity of $T_E = T_2^*$. A comparison of EPI and TURBO-PEPSI images with $T_E = 72.5$ ms revealed very similar activation images.

The gain in sensitivity is particularly advantageous for real time measurements since a change in the relaxation can be effectively ascertained, even with just a few measured values. In summary, it can be said that the multi-echo detection of the differential signal translates into optimal sensitivity for various magnetic field strengths.

Furthermore, the invention can be utilized in echo-planar imaging (EPI), in phase-encoded imaging methods as well as in spectroscopic imaging methods.

The examples presented serve to elucidate the computer and the analysis method on the basis of NMR measurements on the human brain. Naturally, the computer, the nuclear resonance tomograph as well as the analysis method can also be used to examine other samples of either living or non-living material.